Background Document on Gulf War-Related Research

for

The Health Impact of Chemical Exposures During the Gulf War: A Research Planning Conference

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List of Acronyms and Abbreviations

ANG	Air National Guard
ATSDR	Agency for Toxic Substances and Disease Registry
CARC	Chemical Agent Resistant Coating
CCEP	Comprehensive Clinical Evaluation Program
CDC	Centers for Disease Control and Prevention
CIA	Central Intelligence Agency
DHHS	Department of Health and Human Services
DoD	Department of Defense
DSB	Defense Science Board
DU	Depleted Uranium
DVA	Department of Veterans' Affairs
EMG	electromyography
FDA	Food and Drug Administration
GAO	Government Accounting Office
ICD-9	International Classification of Diseases, Ninth Revision
IOM	Institute of Medicine
MCS	Multiple Chemical Sensitivity
MMPI	Minnesota Multiphasic Personality Inventory
NIH	National Institutes of Health
PAC	Presidential Advisory Committee on Gulf War Veterans' Illnesses
PAH	Polycyclic Aromatic Hydrocarbon
PGHR	Persian Gulf Health Registry
PGVCB	Persian Gulf Veterans Coordinating Board
PL	Public Law
PSOB	Presidential Special Oversight Board
RR	rate ratio or relative risk
RWG	Research Working Group
SIU	Special Investigation Unit on Gulf War Illness
SMR	Standardized Mortality Ratios
U.K.	United Kingdom
U.S.	United States
USAEHA	U.S. Army Environmental Hygiene Agency
VA	Veterans' Administration
VOC	Volatile Organic Compound

EXECUTIVE SUMMARY

The purpose of this document is to provide background information to participants in the upcoming conference, *The Health Impact of Chemical Exposures During the Gulf War: A Research Planning Conference*, sponsored by the Centers for Disease Control and Prevention in coordination with the Office of Public Health and Science (Department of Health and Human Services), the National Institutes of Health, and the Agency for Toxic Substances and Disease Registry. In response to U.S. House of Representatives Report 105-205, the conference is to be held on February 28-March 2, 1999 in Atlanta, Georgia for the purpose of obtaining broad public input into the development of a multi-year research plan investigating the relationships of chemical exposures to illnesses among Gulf War veterans.

The 697,000 men and women of U.S. military services who served in the Gulf region in 1990 and 1991 were exposed to a wide array of known and potential hazards to health including blowing dust and sand particles, smoke from oil well fires, petroleum fuels and their combustion products, possible exposure to chemical warfare nerve agents and biological warfare agents, pyridostigmine bromide pills to protect against organophosphate nerve agents, insecticides, vaccinations, infectious diseases, depleted uranium, and psychological and physiological stress. Quantitative data for exposure of soldiers to most of these agents during Gulf deployment, however, are not available. Appendix A of this document gives an account of events related to health concerns of Gulf War veterans. Appendix B discusses what is known concerning exposures and potential health consequences of the most likely health risk factors associated with the Gulf War experience.

Gulf War veterans registered in the U.S. Department of Defense's Comprehensive Clinical Evaluation Program, the U.S. Department of Veterans' Affairs Persian Gulf Health Registry, and the United Kingdom Ministry of Defence Medical Assessment Programme show an array of health symptoms and a distribution of disease diagnoses involving a wide variety of organ systems. In these programs, clinicians were unable to assign a standard diagnostic disease category to about 20-30% of participants other than *symptoms, signs and ill-defined conditions.* Three diagnostic disease categories (*psychological conditions*, *musculoskeletal diseases*, and *symptoms, signs and ill-defined conditions*) represented more than 50% of the primary diagnoses. The overall symptom pattern for Gulf War veterans in the clinical programs has been noted to be consistent with experiences of U.S. veterans of previous wars.

Various review panels and groups have evaluated information regarding illnesses among Gulf War veterans within the past 4-5 years. Appendix A summarizes recommendations from many of these review panels. Given the broad range of illnesses and health symptoms noted among Gulf War veterans and the lack of exposure data, these groups generally have concurred that no single cause of the multiple illnesses could be established. These groups have made several recommendations for research including: 1) epidemiological research to compare prevalence rates of illnesses in Gulf War veterans with appropriate control populations; 2) in-depth neurophysiological, neuropsychological, and psychological evaluations comparing symptomatic

and asymptomatic Gulf War veterans; 3) research on health effects from specific risk factors such as stress, pesticides, depleted uranium, pyridostigmine bromide, and low-level exposure to chemical warfare nerve agents; 4) research on health effects from mixtures of chemicals (e.g., pesticides, pyridostigmine bromide, and chemical warfare nerve agents) alone and in combination with other risk factors; 5) epidemiological research on the health status of U.S. troops known to be in the vicinity of an Iraqi weapons storage site, near Khamisiyah, Iraq, in March 1991 when low-level exposure to sarin and cyclosarin may have occurred compared with troops outside of the area; and 6) research into the causes, methods of prevention, and methods of treatment for musculoskeletal conditions and stress-related disorders.

The U.S.-government sponsored research projects which are coordinated by the Research Working Group of the Persian Gulf Veterans Coordinating Board address a wide spectrum of basic and applied topics related to illnesses among Gulf War veterans. Appendix C describes and evaluates selected published studies related to health concerns of Gulf War veterans. Appendix D contains descriptions of ongoing research projects related to: 1) multiple symptom disorders; 2) genetic differences in susceptibility to chemicals; 3) health effects from mixtures of chemicals and other risk factors; 4) treatment of chronic multiple symptom disorders in Gulf War veterans; 5) health effects from low-level, subclinical exposures to chemical warfare nerve agents; 6) health effects from pyridostigmine bromide; 7) assessment and definition of Gulf War illnesses; 8) prevalence of illnesses and associations between chemical exposures and illnesses in Gulf War veterans; and 9) health effects from depleted uranium exposure.

Published epidemiological studies of mortality rates, rates of hospitalizations, and rates of birth defects after the Gulf War have not found consistent, statistically significant differences between active-duty U.S. military personnel who were deployed to the Gulf War compared with active-duty personnel who were not deployed to the Gulf, except for a higher rate of mortality from unintentional injuries (such as automobile accidents). Further epidemiological research efforts are ongoing to track mortality, hospitalization, and reproductive outcome among groups of Gulf-deployed veterans and non-deployed veterans of the same era.

In contrast to the hospitalization and mortality studies, numerous epidemiological studies of self-reported health symptoms consistently have found statististically significantly higher rates of self-reported symptoms in groups of Gulf-deployed compared with non-deployed veterans and provide evidence that there may be an increased frequency of chronic, multi-systemic conditions of ill health among groups of Gulf War veterans. The array of reported symptoms are, in general, difficult to diagnose into a disease category. The most frequently reported symptoms are similar to the most frequently reported symptoms among veterans diagnosed as having *symptoms, signs and ill-defined conditions* in the previously discussed clinical programs (fatigue, headache, memory problems, sleep disturbances, skin rash, joint or muscle pain, and shortness of breath) and appear to overlap with several of the symptoms in other symptom-based disorders including chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivity. Using a mathematical technique called factor analysis to examine associations among symptoms reported in groups of Gulf War veterans, one group of investigators proposed that there might be unique health

disorders among Gulf War veterans, whereas two other groups of investigators reported finding no evidence of a unique disorder among Gulf War veterans when control groups were included in the analysis.

The lack of exposure data makes it difficult, if not impossible, to know the cause of many of the illnesses among Gulf War veterans. In attempts to obtain clues to possible causes, however, several epidemiological studies are looking for associations between self-reported symptoms and self-reported Gulf War experiences and exposures. To date, a few published studies, mostly of a small scale, have reported some associations between self-reported symptoms and particular risk factors (e.g., receiving multiple vaccinations, exposure to pesticides or debris from Scud missiles), but results are not consistent across studies. Several planned and ongoing research projects are similarly designed to look for possible associations between health symptoms and self-reported exposure to risk factors, including the large-scale Veterans' Administration (VA) National Health Survey. Other ongoing projects are taking a different approach to searching for etiological clues by comparing hospitalization rates, self-reported symptoms, and/or clinical measurements of neurophysiological and neuropsychological variables in various groups of veterans known to be at different geographical locations in March 1991 when low-level exposure to nerve agents may have occurred near the Iraqi weapon storage site near Khamisiyah.

Several hypotheses concerning the cause of difficult-to-diagnose illnesses among some Gulf War veterans remain plausible: some investigators hypothesize physiological changes that are stress-induced; some hypothesize causative relationships to low-level exposure to neurotoxic chemicals; and others hypothesize causative interactions between stress and low-level exposure to mixtures of chemicals. Limited suggestive evidence from a few published animal studies has led some to suggest that delayed neurological effects may occur from short-term exposure to mixtures of anti-cholinesterase agents that may have additive or synergistic effects. To date, the relevance of these animal studies to possible chronic neurological impairment in Gulf War veterans is uncertain for several reasons including the high exposure levels to which the animals were exposed and other potential differences between mixtures to which the animals were exposed and mixtures that may have been experienced by soldiers in the Gulf region. Short-term, high-level exposure to certain carbamate and organophosphate nerve agents is known to produce delayed neurological effects in animals and humans, but the occurrence of delayed effects from short-term, low-level exposure to these types of chemicals (an exposure scenario presumed to be relevant to the Gulf War experience of some veterans) is uncertain. Ongoing research projects at several institutions are evaluating possible delayed effects on neuropathological, neurobehavioral, and immunological variables in several animal species exposed to low-levels of various mixtures of cholinesterase-inhibiting chemicals (e.g., sarin, insecticides, and pyridostigmine), alone and in combination with other risk factors such as stress and vaccinations.

Ongoing basic research projects at several institutions are examining hypotheses related to the biochemical and/or genetic basis for differences among individuals in susceptibility to neurotoxic, cholinesterase-inhibiting chemicals such as organophosphate chemical warfare nerve agents (e.g., sarin) and carbamate anti-nerve-agent drugs (e.g., pyridostigmine bromide). Results from these

projects may lead to new methods to identify individuals at greater risk for neurological effects from cholinesterase-inhibiting chemicals or new prophylactic methods against neurological effects from chemical warfare nerve agents.

Several studies have evaluated neurophysiological and neuropsychological variables in small groups of symptomatic Gulf War veterans, but, in general, have not found obvious or consistent changes. Some of the studies, however, have found subtle changes in several variables in some of the examined patients. Ongoing research projects at numerous institutions are examining a wide range of clinical and laboratory physiological variables in attempts to identify objective diagnostic variables that may be consistently affected in Gulf War veterans experiencing multiple chronic symptoms. Endpoints being evaluated include: brain activation patterns determined with magnetic resonance imaging; nerve firing rate of the peroneal nerve; quantitative electroencephalographic pattern analysis; changes in neurohormonal levels in response to different stressors; cerebral spinal fluid levels of neurotransmitters; pain threshold measurements; esophageal smooth muscle motility; viral infections; immune function; and various physiological responses (e.g., blood pressure, heart rate, eyeblink) to acute physical, chemical, or cognitive challenges. In general, it is believed that this body of research may lead to a better basis for proposing new methods of diagnosis and treatment for Gulf War veterans with multiple unexplained chronic symptoms including fatigue, headache, muscle and joint pain, and chemical sensitivities.

In response to the wide diversity of illnesses and symptoms experienced by Gulf War veterans and the uncertainty of their cause, several reviewers have noted that treatment should proceed on an individual basis. Treatment is best addressed when objective clinical measures of distinct illness can be made, but, in the absence of such measures, multidisciplinary treatment of symptoms may be effective (involving medical evaluations, exercise programs, various therapy programs, and counseling). The U.S. Department of Defense has a Specialized Care Program using such an approach for Gulf War veterans with persistent, non-specific symptoms, and, in collaboration with the Department of Veterans' Affairs, has established a 2-year, multiple-site, control trial of cognitive behavioral therapy, aerobic exercise programs, and usual and customary care for such patients. Two other ongoing treatment trials are based on limited evidence suggesting that some Gulf War veterans with non-specific, chronic symptoms may be infected with microorganisms that are difficult to detect. These are double-blind clinical trials of long-term antibiotic treatment; one with symptomatic patients with positive findings for mycoplasma infection and the other with symptomatic patients with bacterial remnants in their urine.

During the upcoming two-and-a-half day conference, participants from various disciplines will meet several times in Workgroups with the goal of discussing and recommending further research in one of four focus areas related to illnesses among Gulf War veterans:
1) Pathophysiology, Etiology, and Mechanisms of Action; 2) Assessment and Diagnosis;
3) Treatment; and 4) Prevention. Final reports and recommendations from each Workgroup will be presented to the conference at large prior to adjournment.